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<p>Patients present with a differential baseline risk of cancer based on normal and expected variations in genes associated with cancer. The baseline risk of developing cancer is acted on throughout life as the genome of different cells interacts with the environment in the form of exposures (eg, toxins, infections). As genetic damage is incurred throughout a lifetime (directly to DNA sequences or to the epigenome), events are set in motion to progressively disrupt normal cellular pathways toward tumorigenesis. This article attempts to characterize broad categories of genetic aberrations and pathways in a manner that might be useful for the clinician to understand the risk of developing cancer, the pathways that are disrupted, and the potential for molecular-based diagnostics.</p>	
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<p>Strong epidemiologic and molecular data now support the conclusion that human papillomavirus (HPV) infection is responsible for a distinct form of head and neck squamous cell carcinoma (HNSCC), independent from the traditional risk factors of tobacco and alcohol use. Patients with HPV-positive HNSCC have a different clinical presentation and better clinical outcomes than those with HPV-negative HNSCC. A diagnosis of HPV-positive HNSCC is associated not only with therapeutic relevance, but also has important implications for future prevention and screening strategies.</p>	
Human Papillomavirus in HNSCC: A European Epidemiologic Perspective	1143
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<p>The aim of this study was to assess incidence and survival of human papillomavirus-related and unrelated head and neck squamous cell carcinoma sites from 15 European population-based cancer registries. This analysis was performed on 29,265 adult (aged approximately 15 years) cancer patients diagnosed in the period from 1988 to 2002. The human papillomavirus-unrelated cancer sites had an age-standardized incidence higher than the human papillomavirus-related cancer cases (3.8 versus 2.5/100,000 year). Incidence rates of head and neck squamous cell carcinomas increased more for human papillomavirus-related than unrelated</p>	

cancer sites. Three-year survival rates improved more in human papillomavirus-related than unrelated cancer sites, and women had better rates of survival than men.

**Induction Chemotherapy in Locally Advanced Head and Neck Cancer:
A New Standard of Care?**

1155

Jochen H. Lorch, Marshall R. Posner, Lori J. Wirth, and Robert I. Haddad

Locally advanced squamous cell cancer of the head and neck is a major contributor to morbidity and mortality worldwide. Despite progress through the use of multimodality treatment involving surgery, radiotherapy, and chemotherapy in recent years, the survival remains poor, and treatment-related morbidity—mainly caused by radiation-induced effects such as soft tissue scarring, esophageal stenosis, xerostomia, dental decay, and osteoradionecrosis—is a major problem in long-term survivors. Data from early trials and encouraging results from meta-analyses have revived interest in the use of neoadjuvant or induction chemotherapy before definitive local treatment. Recent randomized trials have demonstrated marked improvements in survival with the addition of the taxane docetaxel (Taxotere) to the traditional induction regimen consisting of cisplatin and 5FU (TPF) compared with cisplatin and 5FU (PF) alone and have established a new standard of care. The newer TPF induction chemotherapy regimens also appear to be tolerated better than PF when accompanied by adequate supportive measures. Studies to enhance the efficacy of TPF induction chemotherapy by adding new targeted agents, such as the EGF-R inhibitors cetuximab and panitumumab, are underway.

New Advances in High-Technology Radiotherapy for Head and Neck Cancer

1165

Gregory J. Kubicek and Mitchell Machtay

Radiotherapy has an integral role in the treatment of head and neck cancer. Although radiotherapy has the potential to cure patients with advanced disease it also carries the potential for significant long-term morbidity. New technologies in the setting of head and neck radiotherapy are emerging, which have the potential to increase the cure rate and decrease toxicity. These new technologies include improved radiotherapy treatment design (intensity modulated radiation therapy) and improved planning and implementation (image-guided radiation therapy). Some of these advances are discussed in this article.

Innovation in the Surgical Management of Head and Neck Tumors

1181

Ralph W. Gilbert

The surgical management of head and neck tumors continues to evolve with a focus on reducing treatment-related morbidity. The major changes in the past two decades have been the introduction of function-preserving, minimally invasive surgical approaches and a dramatic change in the ability to reconstruct ablative defects and restore form and function. The future certainly will include better evidence regarding the efficacy and appropriate application of these new techniques. Reconstructive techniques will

continue to evolve with introduction of tissue engineering and cell therapy to further improve the quality of life of patients afflicted with head and neck malignancies.

Incorporation of Molecularly Targeted Agents in the Primary Treatment of Squamous Cell Carcinomas of the Head and Neck

1193

Jacques Bernier

Molecular markers will become increasingly important in directing treatment approaches in locally advanced squamous cell carcinomas of the head and neck (HNSCC). Several predictive markers have been identified that may be useful for selecting tumors most likely to respond to radiotherapy or chemotherapy. However, few markers have potential as therapeutic targets. The epidermal growth factor receptor (EGFR) is the most extensively investigated of these targets in the clinical setting. EGFR inhibitors have demonstrated activity in several studies and the monoclonal antibody cetuximab is currently the only biologic agent approved for the treatment of locally advanced HNSCC in combination with radiotherapy. Another potentially promising approach is the inhibition of vascular endothelial growth factor, alone or in combination with EGFR inhibition.

Molecularly Targeted Agents in the Treatment of Recurrent or Metastatic Squamous Cell Carcinomas of the Head and Neck

1209

Christophe Le Tourneau and Eric X. Chen

Proof of principle that molecularly targeted therapy is a valid therapeutic approach for squamous cell carcinoma of the head and neck (SCCHN) has emerged with epidermal growth factor receptor targeting agents. Other interesting targets, such as Src, insulin-like growth factor 1 receptor, and the proteasome, have been shown in vitro to play key roles in SCCHN, and their inhibition is currently being studied in phase II trials. Identification of predictive biomarkers of resistance or sensitivity to these therapies remains one of the main challenges in the optimal selection of patients most likely to benefit from them. However, clinical trials with these novel agents need to be designed rationally to improve the overall outcome of patients. Given the emerging evidence that human papilloma virus–related SCCHN is a distinct disease, it should be studied in specific trials.

Role of Functional Imaging in Head and Neck Squamous Cell Carcinoma: Fluorodeoxyglucose Positron Emission Tomography and Beyond

1221

Sandro V. Porceddu, Bryan H. Burmeister, and Rodney J. Hicks

Positron emission tomography (PET) has emerged as an integral diagnostic tool in the management of head and neck squamous cell carcinoma (HNSCC). This article reviews the usefulness and ongoing dilemmas of fluorine-18 fluorodeoxyglucose (18-F FDG) PET and FDG PET/CT in HNSCC. In addition, it examines the potential role of novel markers and

biologic characterization of disease, which in the future may assist in targeted therapeutic strategies.

Evaluation of Quality of Life and Organ Function in Head and Neck Squamous Cell Carcinoma

1239

Rosemary Martino and Jolie Ringash

Common concerns of head and neck squamous cell cancer patients include concerns about illness and their future, general physical and emotional well being, speech, body image, and financial issues. Patients receiving radiotherapy report high levels of problems with swallowing, eating, and dry mouth. This article focuses on several of the most common and severe lasting issues for head and neck squamous cell cancer patients: impairments of overall quality of life, xerostomia, speech, and swallowing, focusing primarily on the tools and techniques for measuring such effects.

Understanding the Results of Meta-Analyses in the Treatment of Head and Neck Squamous Cell Cancer

1257

Sebastien J. Hotte and James R. Wright

Clinical trials evaluating therapies in patients who have head and neck cancer are often challenged by low power and competing clinical outcomes, which makes interpretation difficult. Meta-analyses that combine the results of independent trials have the potential to provide high-quality, evidence-based information on what should be considered best practice beyond that of any one trial. In this summary of published meta-analyses, the authors review the evidence supporting the use of concurrent chemotherapy and fractionated radiotherapy for patients who have locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx.

Update on the Management and Therapeutic Monitoring of Advanced Nasopharyngeal Cancer

1267

Herbert H. Loong, Brigitte B. Ma, and Anthony T. Chan

Despite being potentially curable at an early stage, more than 50% of patients who have nasopharyngeal carcinoma present with advanced locoregional disease, which results in a poor prognosis. This article discusses key advancements in the management of nasopharyngeal cancer, including the incorporation of concurrent chemoradiotherapy, new radiotherapy delivery techniques in the form of conformal and intensity-modulated radiotherapy, and salvage options for locoregional recurrence. New cytotoxic and targeted therapies that have resulted in improved survival in the metastatic setting are also described. The use of Epstein-Barr virus DNA for the prognostication and monitoring of nasopharyngeal cancer and the role of new diagnostic imaging techniques are also discussed.

New Agents in the Treatment for Malignancies of the Salivary and Thyroid Glands 1279

Ranee Mehra and Roger B. Cohen

The treatment of relatively rare malignancies, such as those of the salivary glands and iodine refractory thyroid cancer, has been invigorated by the development of novel molecular targeting agents. Accrual to clinical trials for these disease sites continues to be limited by their relatively low incidence. Nonetheless, multicenter collaborations have contributed greatly to the development of a number of emerging systemic therapies. This article briefly summarizes the epidemiology and pathogenesis of salivary gland and thyroid cancer, and then describes some of the new drugs under evaluation for these malignancies.

Sinonasal Malignancies of Neuroendocrine Origin 1297

Danny Rischin and Andrew Coleman

The sinonasal malignancies of putative neuroendocrine origin—esthesioneuroblastoma, sinonasal neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, and sinonasal small cell carcinoma—are uncommon malignancies that frequently present with locally advanced disease. Pathologic distinction between these entities can be difficult, but is important to guide management. These malignancies require complex multimodality treatment and are best managed by multidisciplinary teams in major centers that have expertise in sinonasal malignancies.

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